Y1-08 Young Investigators Day, Sat, Sept 1, 08:30 - 16:40

Stereotactic radiotherapy vs surgery in very early disease. The case for RT

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Lung cancer is the most common cause of cancer death in the world. Approximately 15-20% of non-small cell lung cancer (NSCLC) patients present with early or localized disease. Surgical tumor resection alone is the treatment of choice for this population; surgery alone may produce a local control rate of over 80% and a 5-years survival of 60-70% in patients with NSCLC Stage I. Unfortunately, some patients with early stage NSCLC are not functionally or medically amenable with surgery. For these patients, conventional radiotherapy (RT) represents the alternative treatment but the final results are certainly worse than with surgery, with a local control rate ranging from 40% to 70% and long-term survival of only 5-30%. Several studies reported a benefit with RT dose escalation, suggesting a dose-response relationship in both survival and local control endpoints and showing that doses in the range of 80-100 Gy are able to sterilize a significant proportion of lung cancers [1]. Significant dose intensification to the tumor without increasing the damage to the surrounding normal tissue is very difficult. Dose escalation by conventional RT is limited by long treatment time and volume of normal lung irradiated with high doses of radiation. Significant radiation pneumonitis, arising in 13-37% of patients receiving radical radiation therapy for lung cancer, is certainly the most important factor limiting dose escalation in NSCLC.

One emerging method for shortening the overall treatment time and for sparing functional lung tissue is Stereotactic Body Radiation Therapy (SBRT) [10]. This approach was introduced in clinical use at the Karolinska Hospital in 1991 [8,9] and was significantly based on experience of intracranial Stereotactic Radiosurgery at the same hospital. SBRT offers a non-invasive treatment modality to patients with early stage non small cell lung cancer, not amenable for surgery due to medical reasons or patient's refusal, as well as for lung metastases. Initial clinical results were favourable: local control rates around 90% and 3-years overall survival rates of 66-83% were reported [2-7].

The aim of this prospective study is to analyze feasibility, toxicity and response rate to an expressively designed hypofractionated SBRT regimen.

Materials and Methods: From May 2003 to January 2007, 54 patients with Stage I NSCLC (35 patients with Stage IA disease and 19 patients with Stage IB disease) were treated by SBRT at the University of Turin.

The eligibility criteria for SBRT treatment were (1) Stage I NSCLC, with maximal size lower than 5 cm in diameter, (2) contraindicated or refused surgery, (3) Performance Status ECOG equal or less 2, (4) staging inclusive of CT-PET scan and (5) written informed consent. Patients were immobilized in a stereotactic body frame (ELEKTA® Oncology System) and breathing mobility was reduced mechanically using a "diaphragm control" device, when necessary. Gross Tumor Volume (GTV), Planning Target Volume (PTV) and organs-at-risk were defined in accordance with ICRU-62 on a CT data set acquired with 2.5 mm slices thickness over the whole lungs volume. The PTV included the GTV with a standard margin of 5 mm on axial plan and 10 mm on longitudinal direction. All patients were treated with 45 Gy in 3 fractions over 5 days. The dose was prescribed to the 80% isodose line and delivered with 6-8 non-coplanar static multiple fields of a 10 MV energy Linac.

Dose-Volume Histograms (DVHs), Tumor Control Probability (TCP), Normal Tissue Complication Probability (NTCP) were obtained and evaluated for each case. Early and late toxicities were graded using the Radiation Therapy Oncology Group Radiation Toxicity Scale (RTOG).The follow-up examination included CT scans 45 days after ESRT, every 3 months for the first two years, every 6 months for other three years, CT-PET scan 3 months and then one year after SBRT, and pulmonary function tests every 3 months for the first two years, every 6 months for other three years. Tumor response was evaluated on CT scan using the Response Evaluation Criteria in Solid Tumors (RECIST) [11]. Tumor local control was defined as the absence of progression disease.

Results: Forty-three out of 54 patients were considered for analysis. Nine patients were excluded due to limited follow-up and two patients were lost from follow-up within the study period. The median follow-up time was 16.8 months (range 4.9-43.7 months). Tumor local control was 100%, with 20 complete responses (46.5%), 14 partial responses (32.6%), and 9 patients showing stable disease (20.9%). Fourteen patients with local tumor control developed distant and/or regional failures. At December 2006, thirty-three patients were alive; ten patients died, seven of them for progression disease and three for other reasons not related to neoplastic disease. The disease free survival rates were 80.4% at 12 months and 59% at 24 months; the overall survival rates were 91.6% and 65% at 12 and 24 months, respectively. The disease specific survival rates were 96.9% and 74% at 12 and 24 months, respectively.

The overall toxicity was mild. Three patients experienced slight temporary skin erythema (Grade 1). Clinically significant radiation pneumonitis (RTOG score 3) was observed only in two patients, at 3 and 4.4 months after SBRT; in one of these two patients, concomitant infection was diagnosed. Rib fracture occurred in one patient, presenting with tumor located very close to chest wall; in other three patients with tumor adjacent to chest wall structures, a significant thoracic pain, probably related to high radiation doses received by the peripheral nerves, compared a few months after SBRT. No other treatment-related toxicities have been observed.

Conclusion: SBRT for Stage I NSCLC is a feasible, safe and effective procedure, allowing a significant tumor dose escalation able to achieve tumor control probabilities much more better than with conventional RT. A larger population and a longer follow-up period will be useful to fully assess the clinical benefit of SBRT in early-stage NSCLC as a valid alternative to surgery in medically or functionally unresectable patients. This will also open a possible future scenario for considering SBRT as an alternative to surgery in early stage NSCLC operable patients.

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Y1-09 **Young Investigators Day, Sat, Sept 1, 08:30 - 16:40**

The case for surgery in very early disease

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In 2001, the Japanese Joint Committee of Lung Cancer Registry sent a questionnaire to 320 Japanese institutions regarding the prognosis and clinicopathological profiles of patients who underwent the resection for primary lung neoplasms in 1994. We compiled the data for 7408 patients from 303 institutions (94.7%). Among these, 6644 patients with non-small cell histology were studied in terms of prognosis. The 5-year survival rate of the entire group was 52.6%. The 5-year survival rates by clinical (c-) stage were as follows: 72.1% for IA (n = 2423), 49.9% for IB (n = 1542), 48.7% for IIA (n = 150), 40.6% for IIB (n = 746), 35.8% for IIIA (n = 1270), 28.0% for IIIB (n = 366) and 20.8% for IV (n = 147). The difference in prognosis between neighboring stages was significant except for between IB and IIA and between IIIB and IV. The 5-year survival rates by pathological (p-) stage were as follows: 79.5% for IA (n = 2009), 60.1% for IB (n = 1418), 59.9% for IIA (n = 232), 42.2% for IIB (n = 757), 29.8% for IIIA (n = 1250), 19.3% for IIIB (n = 719) and 20.0% for IV (n = 259). The difference in prognosis between neighboring stages was significant except for between IB and IIA and between IIIB and IV. The survival curves of stages IB and IIA were almost superimposed in both c- and p-settings. Otherwise, the present TNM staging system seemed to well characterize the stage-specific prognosis in non-small cell lung cancer. The T1 descriptor definition and stage grouping for testing was revised as follows. According to the greatest tumor diameter, T1 tumors were divided into T1a tumors (< or =2.0 cm) and T1b tumors (2.1-3.0 cm). With these descriptors, new IA and IB stages were defined as T1a N0 M0, T1b N0 M0, and T2 N0 M0, respectively. For 6644 patients with histologically non-small cell lung cancers resected in 1994 and reported in the Japanese Lung Cancer Registry Study, the survivals and prognostic difference between neighboring stages were studied. The 5-year survival of the entire population was 52.6%. In the clinical setting, the 5-year survivals of the new IA, new IB stages were 77.5% and 69.3%, respectively. In the pathologic setting, they were 83.7% and 76.0%, respectively. For both clinical and pathologic settings, differences between all neighboring stages were statistically significant. Subcategorization of T1 and minor changes in stage grouping results in a system with significant differences in prognosis between neighboring stages. Additionally, the definition of "non-invasive peripheral early cancer" will be reported by Japanese collaboration study in this session

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Adjuvant therapies: what we have learned in the last 5 years

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Following the results of a meta-analysis published 15 years ago, which showed a 5-year survival benefit of approximately 5% for adjuvant chemotherapy in patients with non-small cell lung cancer (NSCLC) [1], various large multicentre studies have investigated the benefit of adjuvant chemotherapy in this disease.

The findings of the above mentioned meta-analysis failed to impact clinical practice, not because the absolute gain was too small but because such an estimate was still imprecise, ranging from 1% detriment to a 10% benefit. In addition, the heterogeneity of surgical procedures and the difference in the staging modalities strongly limit the applicability of the results of this meta-analysis.

Recently published results of five such studies suggest that adjuvant chemotherapy improves survival in patients with stage IIIA and II disease, but not in stage I disease [2-6].

These conclusions have been further supported by a recent meta-analysis of individual patient data - the Lung Adjuvant Cisplatin Evaluation (LACE) - from five large studies (ALPI, ANITA, IALT, JBR.10 and Big Lung Trial [BLT]) [7]. This analysis involved data from 4,584 patients with resected NSCLC who were randomized to adjuvant chemotherapy chemotherapy or no further systemic therapy. In some of these studies, adjuvant radiotherapy was used and left to the discretion of each participating centre. Adjuvant chemotherapy was associated with a significant benefit in overall survival; at 5 years, there was a 5.3% ± 1.6% absolute increase in survival in favor of adjuvant chemotherapy compared with no further systemic therapy. The overall benefit observed varied with stage; there was a significant benefit for patients with stage II and stage III disease whereas there was no significant benefit for those with stage IB disease and an apparent detrimental effect for those with stage IA disease.

In contrast to the findings above, a meta-analysis of several Japanese studies of post-operative adjuvant chemotherapy reported a survival benefit in patients with stage I disease [8]. Of the 2,003 patients studied, 95% had stage I disease. Patients were randomized to receive an oral adjuvant treatment with tegafur in combination with uracil (UFT) for 2 years or no further treatment. The overall survival rates at 5- and 7-years were significantly greater in patients who had received adjuvant chemotherapy than in those who had received surgery alone (81.8% vs 76.5% at 5 years, p = 0.011; 77.2% vs 69.5% at 7 years, p = 0.001).

The concept of relatively mild, low-dose continuous adjuvant therapy is attractive, but the absence of confirmatory adjuvant UFT studies outside Japan strongly limit the applicability of these data in clinical practice because of potential pharmacogenomic differences between Japanese and non-Japanese patients.

In two of the positive studies for adjuvant chemotherapy [4,6], a combination of cisplatin and weekly vinorelbine prolonged survival. These findings led to the conclusion that cisplatin/vinorelbine is a regimen of choice for adjuvant therapies. However, in another adjuvant trial, the combination of cisplatin and vinorelbine did not perform significantly better than any other combination tested [2]. Moreover, when the combination of cisplatin plus a third-generation agent including taxanes, vinorelbine and gemcitabine are compared 'head to head' in the metastatic or locally advanced settings, no significant differences in overall survival are observed.

